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Review Article: Effect Anticancer Drug of Histological Alteration and Improvement their Effects by Natural Antioxidants

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ABSTRACT

Usually, Cancer and anticancer drugs can produce harmful side effects, side effects which occur in tissues or organs and produce adverse histopathological change. Cancer treatment by radiotherapy and chemotherapy, and chemotherapy treatments is more mostly used all over the world. Generally, chemotherapy drugs cusses the damage by free radicals and produce cytotoxicity. Natural antioxidant compounds of daily diet are more effective to scavenge or neutralize the free radicals which create by chemotherapy drugs and finally, improvement histopathological change.

Keywords- Anticancer drugs, Free radicals, Natural antioxidants.

I. INTRODUCTION

Treatment of various cancer disease has been achieved through radiotherapy and chemotherapy, as the occurrence of the cancer disease increasing, chemotherapeutic medicine are more broadly utilized each over the world (Shi *et al.,* 2017). Chemotherapy contains the utilize of chemical managers to growth stop and reduce cancerous cells until at distant places of the primary tumor source. Moreover, it does not separate between a normal and cancer cells, and reduces not only the fast-growth cancer cells but too other fast-growth normal body cells, containing, blood cells and hair (Bonadonna *et al*.,1995; de Graaf *et al.*,1996). Higher than half of all human which detected with cancer illness, take chemotherapy treatment which generally contain drugs to treatment cancer disease in addition to drugs which to assistance completion care the of the cancer management at the dose on timetable (Bonadonna *et al*.,1995; de Graaf *et al.,* 1996). The primary problems to the medical effectiveness of chemotherapy have been the toxicity of the body normal tissues, tissues sites which are multiply rapidly as bone marrow, gastrointestinal tract, hair follicle, oral mucosal lining, etc. are the chief sites of severe toxicity. Cyclophosphamide (CP) drugs produce damage of DNA, mononuclei, predominant lethal mutation, and created free radicals or reactive oxygen species (ROS), Generally damage cusses by free radicals of CP in vivo were genotoxic activity such as chromosome aberration, gene mutation, DNA damages, and sister chromatid exchanges may cusses many of the pathological states having tumor (Abdella, 2008).

Free Radicals are molecules with an unpaired electron, these molecules are very reactive due to the existence free electron in form unpaired and they are intermediated in the natural practices containing cytotoxicity (Khan *et al.,* 2018). Various exogenous sources of free radicals as drugs**,** smoking, water contamination, pesticides, heavy metals**,** industrial solvents, and ultraviolet light **(**Pham-Huy *et al.,* 2008**)**. Free radical are responsible of numerous pathophysiology sickness for threatening people life (Shoker *et al.,* 2023). Biochemical activity which produce free radicals, may produce damage of DNA and breakdown of the membrane lipid (Khan *et al.,* 2018). Most anticancer treatments produce apoptosis by DNA damage (Dickson *et al.,* 2009). As a result, anti-cancer

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drugs which utilized as chemotherapeutic are lethal to normal cells and produce toxicity of immune cells (Azadmehr *et al.*, 2011).

Taking the balanced quantity of nutritious food produce a respectable health, which are scavenging or neutralizing free radicals by natural antioxidants constituents, variation of daily food which have great quantity of vitamin A, C, E, polyphenols, carotenoids, etc. as natural antioxidants compounds, the chief sources of them are vegetables, fruits, beverages , and cereals (Shoker *et al.*, 2023). Therapeutic plants are acknowledged as a rich resource of constituents which used in drug development and manufacture, in addition, several plants are considered as a chief source of diet and these plants are recommended for their useful therapeutic values (Hassan, 2012). Phytochemical screening of medicinal plants has an supplementary great indicator for the invention of other therapies, Phytochemical screening studies of numerous medicinal plants led to the separation of pure bioactive constituents which have been pharmacologically evaluated (Kumar *et al.*, 2015). These compounds such as terpenes, alkaloids, resins, phenols, terpenoids, sterols, steroids, volatile oils, glycosides, and saponins are the chief groups of plant secondary metabolites (Alamgir, 2018). The aim of this review is to reduce a side effects as histopathological which produce from anticancer drugs by natural antioxidant components which occurrence of daily diet variation, because daily food have a great quantities of natural antioxidants constituents.

II. ANTICANCER DRUGS EFFECT 0F HISTOLOGICAL ALTERATION OF LIVER

The liver acts a main character in the metabolisms of a medicines diversity and toxins and therefore are mainly susceptible for deterioration which produced by drugs having cytotoxic chemotherapies system, in addition drug produced liver damage can display a multi-plicative effect, in which this damage may feed-forward resulting in reduced drugs metabolism and their toxicity (Fontana, 2014; Hoofnagle and Björnsson, 2019). Hepatotoxicity as a result from injury to structures such as the liver bile ducts, sinusoids, vasculature, and direct hepatocytes injury. In addition, occlusion of ductal structures and vascular, toxic of metabolite creation, and inflammatory cells infiltration to the liver parenchymal may produce harm (Fontana, 2014; Hoofnagle and Björnsson, 2019).

The hepatocytes parenchymal cells as about 80% of the liver mass, and about 60% of the all number of the adult liver cell population (MacSween et al., 2002; Roy-Chowdhury *et al.*, 2006). Doxorubicin, cisplatin, and fluorouracil (5-FU) drugs have been widely utilized for chemotherapy treatment of several cancers disease containing the liver (Yuan *et al.*, 2008; Lin *et al.*, 2006). Light microscopic showed the higher doses of doxorubicin and cisplatin on male albino rat liver produced great hepatotoxicity compared to 5-FU treatment, having hepatic cords dissolution, necrotic tissues and focal inflammation, low doses of these drugs also displayed abnormal changes, having disintegration of hepatic cords, periportal fibrosis, and arise apoptosis (El-Sayyad *et al.*, 2009).

Apoptosis is a subscriber character of hepatotoxicity which produced through several chemicals, necrosis, as in the hepatotoxicity made through thioacetamide (Ledda-Columbano GM *et al.*, 1991). Anastrozole and tamoxifen are broadly utilized as assistance dealing for breast cancer, and together have been revealed to make fatty liver sickness (Kikuchi *et al* ., 2002). liver section of the mice which were treated with cyclophosphamide drugs showed small necrosis in hepatocyte, small portal space with moderate to severe inflammation, lymphocyte between hepatocytes, dilated and congested sinusoidal space (Shokrzadeh *et al.*, 2014). Al-Salih *et al.*, (2020) Showed when give single dose of Cyclophosphamide drugs of male wister rats, liver lesion was show fatty liver alteration in hepatocytes of liver with occurrence inflammatory cells in hepatic sinusoid too mild liver, but when take double dose of these drugs liver lesion show small focal of liver tissue, this chemotherapy there was more sign appear congested of hepatic blood vessels, early hepatic fibrosis was noted in liver tissue, numbers of collagen fiber and fibroblasts in liver parenchyma, mild liver amyloidosis in both cases.

Medical pointer of cisplatin drugs produced hepatic damage has been explain through increase activities of and bilirubin levels, a serum enzyme, and the jaundice progress (Moriya *et al.*, 2000). Other studies indicated the rats which treated with the anticancer medicines presented a significant reduction in body weight, proposal that hepatotoxicity might have added for this loss (El-Sayyad *et al.*, 2009). Rat dissection indicated that the body weights loss because loss of adipose tissue and skeletal muscles as formerly suggested by Devlin *et al.*, 1997.

Hepatic dysfunction under chemotherapy treatment chiefly involves of abnormal biologic liver assessments showing chronic cholestasis with elevation in the grade of bilirubin, gamma glutamyl transferase (yGT), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) (Kaplowitz, 2007). Drug which induced liver sickness make all forms of chronic and acute hepatobiliary sicknesses, liver damage is labeled hepatocellular when the alanine transaminase (ALT) grade is bigger than 2 times the upper limit of normal, the ALT/alkaline phosphatase (AP) ratio is ≥ 5; when the alkaline phosphatase is bigger than 2 times upper limit of normal, the ALT/AP ratio is ≤ 2; and mixed when the ALT/AP ratio is 2 to 5 and the individual values are more than 2 times upper limit of normal (Kaplowitz, 2001; Lucena *et al.*,2001).

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III. ANTICANCER DRUGS EFFECT OF HISTOLOGICAL ALTERATION OF KIDNEY

The kidney is an important destruction way for several antineoplastic drugs and their metabolites, through tubular secretion and glomerular filtration, chemotherapeutic agents affect of any nephron segment having microvasculature, lead to several medical manifestations as proteinuria, electrolyte disturbances, hypertension, chronic and acute interstitial nephritis, glomerulopathy, acute kidney damage and at times chronic kidney sickness (Santos *et al.*, 2020). Acute kidney damage is a developing problem with adverse economic and medicinal values, the toxicity of anticancer drug remains an important and growing make acute kidney damage, essentially drug which produced acute kidney damage affects all glomerulus, nephron interstitium, segments-vasculature, and tubules (Izzedine and Perazella, 2017). Kidney damage in cancer sick as shown in figure (2).

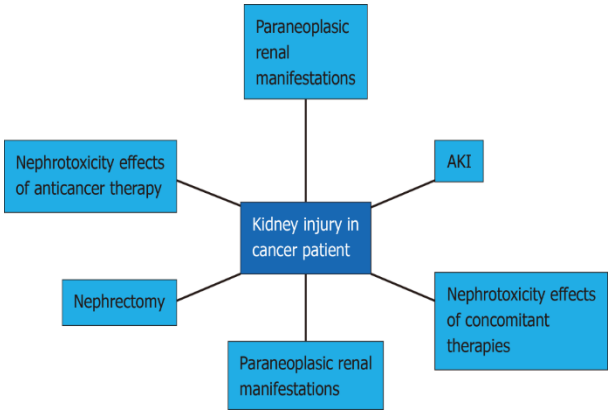

Figure 2: Kidney damage in cancer patient (Jhaveri and Fishbane, 2013)

IV. AKI: ACUTE KIDNEY DISEASE.

Cancer patients can progress a diversity kidney section that impair not only their immediate existence, but also limit the adequate treatment (Lameire, 2014). When administration of cyclophosphamide drugs, kidney section showed tubular injury from the cortex to the medulla and fibrosis (Al-Salih *et al.*, 2020). Anticancer drug toxicity lead to cause acute kidney injury, significantly, drug which induced acute kidney injury affects all nephron segments-vasculature, tubules, interstitium and glomerulus. Modern studies have enlarged understanding into the subcellular drug mechanisms which produce acute kidney injury which contain immune-mediated effects and direct cellular toxicity (Izzedine and Perazella, 2017). Patients identification with high-risk cancer earlier drug exposure can let prevention or at least a decline in the progress and nephrotoxicity severity (Izzedine and Perazella, 2017). Nephrotoxicity is a joint negative effect of several chemotherapeutic agents, greatest usually related with chemotherapy-associated nephrotoxicity are streptozocin, mithramycin, methotrexate, cisplatin, and semustine, also the chemotherapeutic agents have harmful effects on the urothelium and kidneys which cause cystic change, urothelial changes, papillary necrosis, interstitial nephritis, haemorrhagic cystitis is described by epithelial proliferation, acute tubular necrosis, and infarction (Jia *et al.*, 2015). Interstitial nephritis may be related with a weakening in eosinophiluria, creatinine clearance, proteinuria, and eosinophilia, several of chemotherapy have been related with interstitial nephritis, greatest especially ipilimumab which arouse interstitial nephritis, ill are treated with prednisone and come back rapidly to their standard kidney function (Izzedine *et al.*, 2014).

V. ANTICANCER DRUGS EFFECT OF HISTOLOGICAL ALTERATION OF INTESTINE

The small intestine is a actual essential organ and acts several main functions in the body of human (Xie *et al.*, 2016). Treatment of several cancer has been done through radiotherapy and chemotherapy as the occurrence of cancer rises chemotherapeutic medicines are suitable most broadly utilized all over the world (Shi *et al.*, 2017). Cyclophosphamide is an active anticancer drug utilized in the treatment various cancers kinds as breast cancer, multiple myeloma, acute and chronic ovarian carcinoma, leukemia, lymphomas, sarcoma, and neuroblastoma (Nabil *et al.*, 2020). It is too utilized as an immune - suppressant for treating of autoimmune illnesses (Madondo *et al.*, 2016). Single intraperitoneal injection of cyclophosphamide drugs origins great in the intestinal mucosa distruction (Abdel-Hafez *et al.*, 2021). High doses of Cyclophosphamide drugs cause intestinal mucosa damage that leading to medical problems as diarrhea, dyskinesia, and bacterial translocation (Owari *et al.*, 2012), and they make severe oxidative stress of tissue and great cellular damage, increasing apoptosis, healthy of cells and death cancer (AbdelHafez *et al.*, 2017).

VI. IMPROVEMENT THE HISTOLOGICAL ALTERATIONS BY NATURAL ANTIOXIDANTS

Free radical can responsible of numerous pathophysiology sickness for threatening people life, and they are created from exogenous, and endogenous sources, balanced amount utilizing of daily food lead to a good health, can scavenging or neutralizing free radicals through natural antioxidants constituents, daily food contain a great amount of polyphenols, carotenoids, vitamin A, E and C, etc. as natural antioxidants

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compounds, the chief bases of them are fruits, vegetables, cereals, and beverages (Shoker *et al.,* 2023). Khodeer *et al.,* (2020) detected together hepatic and pancreatic tissues involved congested vessels, architecture disturbance, inflammatory infiltrates, hydropic degeneration, and as well as increased fragmentation of DNA in cyclophosphamide-treated mice, while pretreatment with Evening primrose oil was displayed significant improvement histopathological changes and DNA fragmentation in mice.

Several plants utilized in traditional medication have antimutagenic and anticarcinogenic effects (Ozioma and Chinwe, 2019). Natural antioxidants included spices support to reduce oxidative stress (Bi *et al.,* 2017). *Cinnamomum cassia* may be an active drug to prevent cancer or another type of illness which lead to damage genetic materials (Ambasta et al., 2017).

Phytochemical screening of medicinal plants has an supplementary high indicator for the discovery of new therapy, chemical studies of numerous medicinal plants led to the separation of pure bioactive compounds which have been pharmacologically evaluated (Kumar *et al.,* 2015). These compounds such as resins, terpenes, phenols, terpenoids, alkaloids, steroids, sterols, saponins, volatile oils, and glycosides are the chief groups of plant secondary metabolites (Alamgir, 2018). Some studies indicated that the mice which were treated with aqueous, phenolic, AgNPs of *S. officinalis*, *Cinnamomum cassia* plant the enhanced liver histopathological alterations which induced by cyclophosphamide (Shoker, 2021).

Kouame *et al.,* (2018) indicated *C. cassia* silver nanoparticles AgNPs capable to decrease the histomorphological changes following STZ-induced diabetes, probably performing by oxidant/antioxidant pathways. Repeated administration for ivermectin of rabbit creates damaging effects on kidney function and numerous histopathological changes were discovered in kidney and lung structure, and while administration the vitamin C acts as defensive agent (Al-Jassim *et al.,* 2016).The results showed the triglycerides, total cholesterol, AST, ALP, and ALT were significantly rises in mice which treated with cyclophosphamide, while when administration, aqueous, phenolic, NPs aqueous extract of *S. officinalis* this parameters decrease significantly (Shoker, *et al.,* 2020). Natural antioxidants of plants were the molecule which may be capable to donate electron to free radicals and produce neutralization of free radicals (Gbadamosi and Yekini, 2016).

VII. CONCLUSION

Improvement histopathological change which induced by chemotherapy drugs through increase taking daily diet, due to plants have natural antioxidant compounds which are more effective to neutralize or scavenge the free radicals which produce from chemotherapy drugs.

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